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(54) Title: USE OF CEPHEM DERIVATIVES AS ANTI-METASTATIC AGENTS			
(57) Abstract  The present invention relates to the use of known cephem derivatives of formula (I), wherein n is zero, one or two; R <sup>1</sup> is hydrogen or an organic radical, R <sup>2</sup> represents halo or an organic radical or R <sup>1</sup> and R <sup>2</sup> taken together with the C-2 carbon atom of the cephem nucleus constitute a carbocyclic or heterocyclic group; R <sup>3</sup> represents R <sup>2</sup> as defined above or an organic radical, R <sup>4</sup> is either R <sup>1</sup> or an organic group, R <sup>5</sup> is either R <sup>1</sup> as defined above or halo or C <sub>1</sub> -C <sub>6</sub> alkoxy, C <sub>1</sub> -C <sub>6</sub> alkylthio or C <sub>1</sub> -C <sub>6</sub> acylamino; R <sup>6</sup> is R <sup>2</sup> as defined above or an organic group, or pharmaceutically acceptable salt thereof.			
 (I)			

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**"USE OF CEPHEM DERIVATIVES AS ANTI-METASTATIC AGENTS"**

The present invention relates to the use of cephem derivatives as anti-metastatic agents.

5 As known, malignancy of cancer is mainly due to metastasis. Because therapy usually fails to destroy multiple secondary tumor, their uncontrolled growth leads to death of patients. Only very few patients die from complications directly arising from primary tumor.

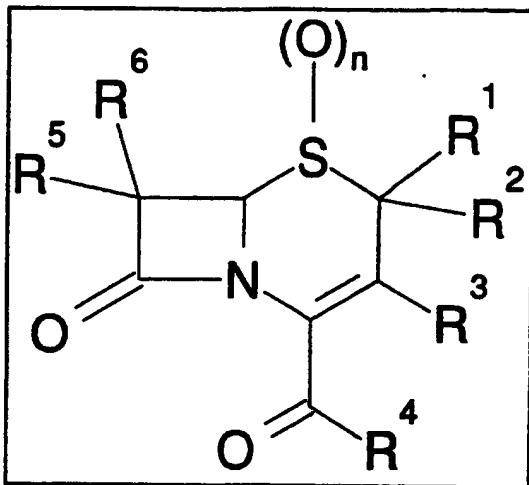
10 Accordingly, there is a need in therapy of drugs able to prevent and/or block the metastatic spread.

Several cephem derivatives were described as having elastase inhibiting activity and can be used in the treatment of inflammatory and degenerative diseases 15 caused by proteolytic enzymes in mammals including humans.

Now we have found that a selected class of compounds previously disclosed can prevent and/or block the metastatic spread of tumors in mammals, including 20 humans.

Accordingly one object of the present invention is the use of a compound of formula (I)

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wherein n is zero, one or two;

R<sup>1</sup> is hydrogen or an optionally substituted C<sub>1</sub>-C<sub>12</sub> alkyl, C<sub>2</sub>-C<sub>12</sub> alkenyl, C<sub>2</sub>-C<sub>12</sub> alkynyl, C<sub>6</sub>-C<sub>10</sub> aryl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>5</sub>-C<sub>8</sub> cycloalkenyl, or C<sub>7</sub>-C<sub>14</sub> aralkyl, C<sub>8</sub>-C<sub>14</sub> 5 aralkenyl, C<sub>8</sub>-C<sub>14</sub> aralkynyl, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, heterocyclyl, (heterocyclyl)alkyl, (heterocyclyl)alkenyl;

R<sup>2</sup> represents an atom or group selected from the following:

- 10 (1) halogen
- (2) R<sup>1</sup> as defined above
- (3) an ether OR<sup>1</sup> wherein R<sup>1</sup> is as defined above
- (4) a thioether, sulphoxide or sulphone -S(O)<sub>n</sub>R<sup>1</sup> wherein n and R<sup>1</sup> are as defined above
- 15 (5) acyloxy -OC(O)R<sup>1</sup> wherein R<sup>1</sup> is as defined above;
- (6) sulphonyloxy -OS(O)<sub>2</sub>R<sup>1</sup> wherein R<sup>1</sup> is as defined

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above;

or R<sup>1</sup> and R<sup>2</sup> taken together form a methylene group of formula =CHR<sup>1</sup> or =CH-CO<sub>2</sub>R<sup>1</sup> or =CH-COR<sup>1</sup> wherein R<sup>1</sup> is as defined above; or R<sup>1</sup> and R<sup>2</sup> taken together with the C-2  
5 carbon atom of the cephem nucleus constitute a carbocyclic or heterocyclyl group;

R<sup>3</sup> represents one of the following:

- (1) R<sup>2</sup> as defined above
- (2) an acyl group -C(O)R<sup>1</sup>, -C(O)OR<sup>1</sup> or -CO<sub>2</sub>H wherein R<sup>1</sup>  
10 as defined above
- (3) an oxymethyl group -CH<sub>2</sub>-OR<sup>1</sup> wherein R<sup>1</sup> is as defined above
- (4) a thiomethyl group or a derivative thereof of formula -CH<sub>2</sub>S(O)<sub>n</sub>R<sup>1</sup> wherein n and R<sup>1</sup> are as defined  
15 above
- (5) an acyloxymethyl group -CH<sub>2</sub>OC(O)R<sup>1</sup> wherein R<sup>1</sup> is as defined above or a -CH<sub>2</sub>O-R<sup>7</sup> wherein R<sup>7</sup> is a mono, di- or tripeptide composed of D or L α-aminoacids chosen from Ala, Gly, Val, Leu, Ile,  
20 Phe and with the terminal amino group either free or protected as an amide -NHCOR<sup>1</sup> or sulfonamide -NHSO<sub>2</sub>R<sup>1</sup> wherein R<sup>1</sup> is as defined above
- (6) an acylthiomethyl group -CH<sub>2</sub>SC(O)R<sup>1</sup> wherein R<sup>1</sup> is as defined above
- (7) a sulphonyloxymethyl group -CH<sub>2</sub>-OSO<sub>2</sub>R<sup>1</sup> wherein R<sup>1</sup> is  
25 as defined above

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(8) a group of formula  $-\text{CH}_2-\text{Z}-\text{NR}^1\text{R}^8$  wherein Z is a bond,  $-\text{O C(O)}-$  or  $-\text{OS(O)}_2-$ ,  $\text{R}^1$  is as defined above and  $\text{R}^8$ , being the same or different, is as defined above for  $\text{R}^1$ ; or  $\text{R}^1$  and  $\text{R}^8$  taken together with the nitrogen atom to which they are attached represent a heterocyclic ring;

(9) ammoniomethyl  $-\text{CH}_2\text{N}^+\text{R}^1\text{R}^8\text{R}^9$  wherein  $\text{R}^1$  and  $\text{R}^8$  are as defined above and  $\text{R}^9$ , being the same or different, is as defined for  $\text{R}^1$ ; or  $\text{R}^1$  is alkyl and  $\text{R}^8$  and  $\text{R}^9$  together with the nitrogen atom to which they are attached represent a heterocyclic ring;

$\text{R}^4$  is either:

(1) a group  $\text{R}^1$  wherein  $\text{R}^1$  is as defined above

(2) a group  $\text{OR}^1$  wherein  $\text{R}^1$  is as defined above

(3) a group  $\text{SR}^1$  wherein  $\text{R}^1$  is as defined above

(4) a group  $\text{NR}^1\text{R}^5$  wherein  $\text{R}^1$  and  $\text{R}^8$  are as defined above;

$\text{R}^5$  is either  $\text{R}^1$  as defined above or halogen or  $\text{C}_1\text{-C}_6$  alkoxy,  $\text{C}_1\text{-C}_6$  alkylthio or  $\text{C}_1\text{-C}_6$  acylamino;

$\text{R}^6$  is a group selected from the following:

(1)  $\text{R}^2$  as defined above

(2) a group of formula  $-\text{Z-N(R}^1)\text{R}^8$  wherein Z,  $\text{R}^1$  and  $\text{R}^8$  are as defined above

(3) a group of formula  $-\text{NR}^8\text{C(O)R}^1$  wherein  $\text{R}^1$  and  $\text{R}^8$  are as defined above, or  $\text{R}^1$  and  $\text{R}^8$  taken together with

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the aminocarbonyl group to which they are attached  
constitute a heterocyclic ring

(4) an acylamino group  $-NHR^7$  wherein  $R^7$  is as defined  
above

5 (5) an ammonio group  $-N^+R^1R^8R^9$  wherein  $R^1$ ,  $R^8$  and  $R^9$  are  
as defined above;

or  $R^5$  and  $R^6$  taken together with the C-7 carbon atom of  
the cephem nucleus constitute a carbocyclic or  
heterocyclic ring;

10 or  $R^5$  and  $R^6$  taken together constitute a methylene group  
of formula  $=CHR^1$ ,  $=CH-CO-R^1$  or  $=CH-SO_2R^1$  wherein  $R^1$  is as  
defined above

or a pharmaceutically acceptable salt thereof, in the  
preparation of a medicament for use in preventing  
15 and/or treating the metastatic spread of tumors.

A further object the present invention is to provide a  
compound of formula (I), as defined above, or a  
pharmaceutically acceptable salt thereof, for use in  
preventing and/or treating the metastatic spread of  
20 tumors.

The  $C_1-C_{12}$  alkyl group is a straight or branched alkyl  
group such as methyl, ethyl, n-propyl, isopropyl,  
n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl,  
n-hexyl and so on.

25 The  $C_2-C_{12}$  alkenyl group is a straight or branched  
alkenyl group such as vinyl, allyl, crotyl,

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2-methyl-1-propenyl, 1-methyl-1-propenyl, butenyl, pentenyl and so on.

The C<sub>2</sub>-C<sub>12</sub> alkynyl group is a straight or branched alkynyl group such as ethynyl, propargyl, 1-propynyl, 5 1-butynyl, 2-butynyl and so on.

The C<sub>6</sub>-C<sub>10</sub> aryl group is a monocyclic or bicyclic aromatic

hydrocarbon group of 6 to 10 carbon atoms, such as phenyl and naphtyl.

10 The C<sub>3</sub>-C<sub>8</sub> cycloalkyl group is a saturated carbocyclic group of 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and so on.

15 The C<sub>5</sub>-C<sub>8</sub> cycloalkenyl group is an unsaturated carbocyclic group such as cyclopentenyl, cyclohexenyl and so on.

The C<sub>7</sub>-C<sub>14</sub> aralkyl group is an alkyl group of 1 to 4 carbon atoms linked to a monocyclic or bicyclic aromatic hydrocarbon group of 6 to 10 carbon atoms.

Examples of aralkyl groups are benzyl, phenylethyl and 20 naphtylmethyl.

The C<sub>8</sub>-C<sub>14</sub> aralkenyl group is an alkenyl group of 2 to 4 carbon atoms linked to a monocyclic or bicyclic aromatic hydrocarbon group of 6 to 10 carbon atoms.

Examples of aralkenyl groups are styryl, 25 2-phenyl-1-propenyl, 3-phenyl-2-butenyl, 2-naphtylethenyl and so n.

The C<sub>8</sub>-C<sub>14</sub> aralkynyl group is an alkynyl group of 2 to

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4 carbon atoms linked to a monocyclic or bicyclic aromatic hydrocarbon group of 6 to 10 carbon atoms.

Examples of aralkynyl groups are 2-phenylethynyl, 2-naphtylethynyl and so on.

5 The (cycloalkyl)alkyl group is an alkyl group of 1 to 4 carbon atoms linked to a cycloalkyl group.

The (cycloalkyl)alkenyl group is an alkenyl group of 2 to 4 carbon atoms linked to a cycloalkyl group or to an aryl group.

10 The heterocyclyl group is a 3- to 6-membered, saturated or unsaturated heterocyclyl ring, containing at least one heteroatom selected from O, S and N, which is optionally fused to a second 5- or 6-membered, saturated or unsaturated heterocyclyl group or to a cycloalkyl group or to an aryl group.

15 In particular, the heterocyclyl group may be for example a tetrazole, thiadiazole, pyrrole, triazole, imidazole, oxazole, thiophene, pyridine, pyrazine, triazine, morpholine and the like.

20 The (heterocyclyl)alkyl group is an alkyl group of 1 to 4 carbon atoms linked to a heterocyclyl group.

The (heterocyclyl)alkenyl group is an alkenyl group of 2 to 4 carbon atoms linked to a heterocyclic group.

25 The term halogen (or halo) preferably encompasses fluorine, chlorine or bromine.

The C<sub>1</sub>-C<sub>6</sub> alkoxy group is a straight or branched alkylthio group such as methoxy, ethoxy, n-propoxy,

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isopropoxy, n-butoxy, isobutoxy, sec-butoxy,  
tert-butoxy, n-pentoxy, n-hexyloxy and so on.

The C<sub>1</sub>-C<sub>6</sub> alkylthio group is a straight or branched  
alkoxy group such as methylthio, ethylthio,  
5 n-propylthio, isopropylthio, n-butylthio, isobutylthio,  
sec-butylthio, tert-butylthio, n-pentylthio,  
n-hexylthio and so on.

The C<sub>1</sub>-C<sub>6</sub> acylamino group is a straight or branched  
acylamino group such as formamido, acetamido,  
10 propionamido, pivalamido and so on.

The above said alkyl, alkenyl, alkynyl, cycloalkyl,  
cycloalkenyl, aryl, aralkyl, aralkenyl, aralkynyl,  
(cycloalkyl)alkyl, (cycloalkyl)alkenyl, heterocyclyl,  
(heterocyclyl)alkyl, (heterocyclyl)alkenyl, alkoxy,  
15 alkylthio, acylamino groups can be either unsubstituted  
or substituted by one or more substituents selected  
from the following ones:

- halo (i.e., fluoro, bromo, chloro or iodo);
- hydroxy or oxo;
- 20 - nitro;
- azido;
- mercapto (-SH);
- amino (i.e., -NH<sub>2</sub>, or -NHR' or -NR'R'') wherein R'  
and R'', which are the same or different, are C<sub>1</sub>-C<sub>12</sub>
- 25 straight or branched alkyl or phenyl or benzyl;
- formyl (i.e., -CHO);

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- cyano;
- carboxy(alkyl) (i.e.,  $(\text{CH}_2)_t\text{COOH}$  or  $(\text{CH}_2)_t\text{COOR}'$ )  
wherein R' is as defined above and t is 0, 1, 2 or 3;
- sulpho (i.e.,  $-\text{SO}_3\text{H}$ );
- 5 - acyl (i.e.,  $-\text{C}(\text{O})\text{R}'$ ) wherein R' is as defined above  
or trifluoroacetyl (i.e.,  $-\text{C}(\text{O})\text{CF}_3$ );
- carbamoyl (i.e.,  $-\text{CONH}_2$ ); N-methylcarbamoyl (i.e.,  
 $-\text{CONHCH}_3$ ) or N-carboxymethylcarbamoyl (i.e.,  
 $-\text{CONHCH}_2\text{COOH}$ );
- 10 - carbamoyloxy (i.e.,  $-\text{OCONH}_2$ );
- acyloxy (i.e.,  $-\text{OC}(\text{O})\text{R}'$ ) wherein R' is as defined  
above or formyloxy (i.e.,  $-\text{OC}(\text{O})\text{H}$ );
- alkoxy carbonyl or benzyloxycarbonyl (i.e.,  $-\text{C}(\text{O})\text{OR}'$ )  
wherein R' is as defined above;
- 15 - alkoxy carbonyloxy or benzyloxycarbonyloxy (i.e.,  
 $-\text{OC}(\text{O})\text{OR}'$ ) wherein R' is as defined above;
- alkoxy, phenoxy or benzyloxy (i.e.,  $-\text{OR}'$ ) wherein R'  
is as defined above;
- alkylthio, phenylthio or benzylthio (i.e.,  $-\text{SR}'$ )  
20 wherein R' is as defined above;
- alkylsulphinyl, phenylsulphinyl or benzylsulphinyl  
(i.e.,  $-\text{S}(\text{O})\text{R}'$ ) wherein R' is as defined above;
- alkylsulphonyl, phenylsulphonyl or benzylsulphonyl  
(i.e.,  $-\text{S}(\text{O})_2\text{R}'$ ) wherein R' is as defined above;
- 25 - acylamino (i.e.,  $-\text{NHC}(\text{O})\text{R}'''$  or  $-\text{NHC}(\text{O})\text{OR}'''$ ) wherein  
R''' is C<sub>1</sub>-C<sub>12</sub> straight or branched alkyl, phenyl,  
benzyl,  $\text{CH}_2\text{CH}_2\text{COOH}$  or  $\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$ ;

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- sulphonamido (i.e.,  $-\text{NHSO}_2\text{R}'$ ) wherein  $\text{R}'$  is as defined above;
- guanidino (i.e.,  $-\text{NHC}(=\text{NH})\text{NH}_2$ );
- $\text{C}_1\text{-C}_4$  alkyl,  $\text{C}_2\text{-C}_4$  alkenyl or alkynyl;
- 5 -  $\text{C}_3\text{-C}_6$  cycloalkyl;
- phenyl
- substituted methyl selected from chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, aminomethyl,  $\text{N,N}$ -dimethylaminomethyl, azidomethyl,
- 10 cyanomethyl, carboxymethyl, sulphomethyl, carbamoylmethyl, carbamoyloxymethyl, hydroxymethyl,  $\text{C}_1\text{-C}_4$  alkoxy carbonylmethyl, guanidinomethyl.

The carboxyl-protecting group may, for example, be a lower alkyl group such as methyl, ethyl, propyl, isopropyl or tert-butyl; a halogenated lower alkyl group such as a 2,2,2-trichloroethyl or a 2,2,2-trifluoroethyl; a lower alkanoyloxyalkyl group such as acetoxyethyl, propionyloxymethyl, pivaloyloxymethyl, 1-acetoxyethyl, 1-propionyloxyethyl; 20 a lower alkoxy carbonyloxyalkyl group such as 1-(methoxy carbonyloxy)ethyl, 1-(ethoxy carbonyloxy)ethyl, 1-(isopropoxycarbonyloxy)ethyl; a lower alkenyl group such as 2-propenyl, 2-chloro-2-propenyl, 3-methoxycarbonyl-2-propenyl, 2-methyl-2-propenyl, 25 2-butenyl, cinnamyl; an aralkyl group such as benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, o-nitrobenzyl,

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p-nitrobenzyl, benzhydryl, bis(p-methoxyphenyl)methyl; a (5-substituted 2-oxo-1,3-dioxol-4-yl)methyl group such as (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl; a lower alkylsilyl group such as trimethylsilyl,  
5 tert-butyldimethylsilyl, tert-butyldiphenylsilyl, triphenylsilyl; or an indanyl group; a phtalidyl group; a pyranyl group; a metoxymethyl or methylthiomethyl group; a 2-methoxyethoxymethyl group. Particularly preferred are a tert-butyl group, a p-nitrobenzyl group,  
10 a p-methoxybenzyl group, a benzhydryl group, a tert-butyldimethylsilyl, tert-butyldiphenylsilyl group or a propenyl group.

The amino, hydroxy or mercapto protecting groups possibly present may be those usually employed in the  
15 chemistry of penicillins and cephalosporins for this kind of functions. They may be, for instance, optionally substituted, especially halo-substituted, acyl groups, e.g. acetyl, monochloroacetyl, dichloroacetyl, trifluoroacetyl, benzoyl or  
20 p-bromophenacyl; triarylmethylgroups, e.g. triphenylmethyl; silyl groups, in particular trimethylsilyl, dimethyl-tert-butylsilyl, diphenyl-tert-butylsilyl; or also groups such as tert-butoxycarbonyl, p-nitrobenzyloxycarbonyl,  
25 2,2,2-trichloroethoxycarbonyl, benzyl and pyranyl. Preferred protecting groups of the hydroxy function are p-nitrobenzyloxycarbonyl; allyloxycarbonyl;

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dimethyl-tert-butylsilyl; diphenyl-tert-butylsilyl;  
trimethylsilyl; 2,2,2-trichloroethoxycarbonyl; benzyl;  
dimethoxybenzyl; p-methoxybenzyloxycarbonyl;  
p-bromophenacyl; triphenylmethyl, pyranyl,  
5 methoxymethyl, benzhydryl, 2-methoxyethoxymethyl,  
formyl, acetyl, trichloroacetyl.

As already said, the invention includes within its scope

the salts of those compounds of formula (I) that have  
10 salt-forming groups, especially the salts of the compounds having a carboxylic group, a basic group (e.g. an amino or guanidino group), or a quaternary ammonium group. The salts are especially physiologically tolerable salts, for example alkali metal and alkaline earth metal salts (e.g. sodium, potassium, lithium, calcium and magnesium salts), ammonium salts and salts with an appropriate organic amine or amino acid (e.g. arginine, procaine salts), and the addition salts formed with suitable organic or  
15 inorganic acids, for example hydrochloric acid, sulphuric acid, carboxylic and sulphonic organic acids (e.g. acetic, trifluoroacetic, p-toluensulphonic acid). Some compounds of formula (I) which contain a carboxylate and an ammonium group may exist as  
20 zwitterions; such salts are also part of the present invention.

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The present invention encompasses all the possible stereoisomers as well as their racemic or optically active mixtures.

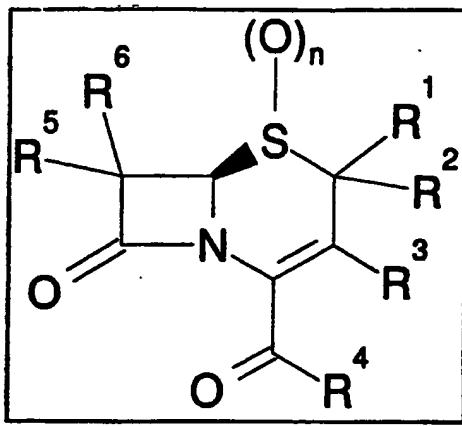
Furthermore, physiologically hydrolizable esters, 5 hydrates and solvates of compounds of formula (I) are included within the scope of the present invention.

The physiologically hydrolizable esters of the compounds (I) may include, for example, methoxycarbonylmethyl, 1-methoxycarbonyloxy-1-ethyl, 10 indanyl, phtalidyl, methoxymethyl, pivaloyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl or 5-methyl-2-oxo-1,3-dioxolan-4-yl esters, and other physiologically hydrolizable esters which have been widely used in the technical fields of penicillin and cephalosporin 15 antibiotics: more preferably, methoxycarbonyloxymethyl, 1-methoxycarbonyloxy-1-ethyl, methoxymethyl or pivaloyloxymethyl; and most preferably, methoxycarbonyloxymethyl or methoxymethyl.

Typical solvates of the cephalosporin compounds of 20 formula(I) may include solvates with water miscible solvents, e.g. methanol, ethanol, acetone or acetonitrile or acetonitrile; and more preferably, ethanol.

Preferred compounds of formula (I), according to the 25 invention, are the compounds of the formula (Ia)

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wherein n, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup>, are as defined above, and the pharmaceutically acceptable salts thereof. Examples of compounds according to the present invention are the following:

- 5      1) (6R,7S)-2-(2,2-Dimethyl-propionyl)-4-(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-[1,2,4]triazin-3-ylsulfanyl)-7-methoxy-3-methyl-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one
- 10     2) 2-Benzoyl-7-methoxy-4-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanyl)-3-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanylmethyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one
- 15     3) 2-(2,2-Dimethyl-propionyl)-7-methoxy-4-(1-methyl-1H-tetrazol-5-ylsulfanyl)-3-(1-methyl-1H-tetrazol-5-ylsulfanylmethyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one
- 20     4) 2-Benzoyl-4-(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-[1,2,4]triazin-3-ylsulfanyl)-7-methoxy-3-methyl-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one
- 20     5) 2-Benzoyl-7-methoxy-3-methyl-4-(1-methyl-1H-

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tetrazol-5-ylsulfanyl)-5,5-dioxo-5-thia-1-aza-  
bicyclo[4.2.0]oct-2-en-8-one  
6) 2-(2,2-Dimethyl-propionyl)-7-methoxy-3-methyl-4-(5-  
methyl-[1,3,4]thiadiazol-2-ylsulfanyl)-5,5-dioxo-5-  
5 thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one  
7) 2-(2,2-Dimethyl-propionyl)-7-methoxy-4-(5-methyl-  
[1,3,4]thiadiazol-2-ylsulfanyl-3-(5-methyl-  
[1,3,4]thiadiazol-2-ylsulfanylmethyl)-5,5-dioxo-5-thia-  
1-aza-bicyclo[4.2.0]oct-2-en-8-one  
10 8) 2-Benzoyl-7-methoxy-4-(1-methyl-1H-tetrazol-5-  
ylsulfanyl)-3-(1-methyl-1H-tetrazol-5-  
ylsulfanylmethyl)-5,5-dioxo-5-thia-1-aza-  
bicyclo[4.2.0]oct-2-en-8-one  
9) 7-Allyl-2-benzoyl-4-(5-methyl-[1,3,4]thiadiazol-2-  
15 ylsulfanyl)-3-(5-methyl-[1,3,4]thiadiazol-2-  
ylsulfanylmethyl)-5,5-dioxo-5-thia-1-aza-  
bicyclo[4.2.0]oct-2-en-8-one  
10) 7-Allyl-2-(2,2-dimethyl-propionyl)-4-(5-methyl-  
[1,3,4]thiadiazol-2-ylsulfanyl)-3-(5-methyl-  
20 [1,3,4]thiadiazol-2-ylsulfanylmethyl)-5,5-dioxo-5-thia-  
1-aza-bicyclo[4.2.0]oct-2-en-8-one  
11) 3-(6-Hydroxy-2-methyl-5-oxo-2,5-dihydro-  
[1,2,4]triazin-3-ylsulfanylmethyl)-7-methoxy-5,5-dioxo-  
2-(pyrrolidine-1-carbonyl)-5-thia-1-aza-  
25 bicyclo[4.2.0]oct-2-en-8-one  
12) 1-(3-Acetoxyethyl-7-methoxy-5,5,8-trioxo-5-thia-1-  
aza-bicyclo[4.2.0]oct-2-enan-2-carbonyl)pyrrolidine-2-

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carboxilic acid

13) 1-[3-Acetoxymethyl-5,5,8-trioxo-7-(2,2,2-trifluoro-  
ace tylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-enane-2-  
carbonyl]-pyrrolidine-2-carboxilic acid

5 14) 1-(7-Benzoylamino-3-methyl-5,5,8-trioxo-5-thia-1-  
aza-bicyclo[4.2.0]oct-2-enane-2-carbonyl)-pyrrolidine-  
2-carboxylic acid

15) 3-Methyl-5,5,8-trioxo-5-thia-1-aza-  
bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 4-carboxy-  
10 benzyl ester

16) 2-Benzoyl-7-ethylsulfanyl-4-(5-methyl-  
[1,3,4]thiadiazol-2-ylsulfanyl)-3-(5-methyl-  
[1,3,4]thiadiazol-2-ylsulfanylmethyl)-5,5-dioxo-5-thia-  
1-aza-bicyclo[4.2.0]oct-2-en-8-one

15 17) 2-Benzoyl-7-ethylsulfanyl-3-methyl-4-(5-methyl-  
[1,3,4]thiadiazol-2-ylsulfanyl)-5,5-dioxo-5-thia-1-aza-  
bicyclo[4.2.0]oct-2-en-8-one

18) 3-(1-Methyl-1H-tetrazol-5-ylsulfanylmethyl)-5,5,8-  
trioxo-7-(2,2,2-trifluoro-acetylarnino)-5-thia-1-aza-  
20 bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 4-carboxy-  
benzyl ester

19) 2-Acetylarnino-3-[7-methoxy-3-(1-methyl-1H-tetrazol-  
5-ylsulfanylmethyl)-5,5,8-trioxo-5-thia-1-aza-  
bicyclo[4.2.0]oct-2-enane-2-carbonylsulfanyl]-propionic  
25 acid

20) 2-Acetylarnino-3-[7-allyl-3-(1-methyl-1H-tetrazol-5-  
ylsulfanylmethyl)-5,5,8-trioxo-5-thia-1-aza-

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bicyclo[4.2.0]oct-2-enane-2-carbonylsulfanyl]-propionic acid

and the pharmaceutically acceptable salts thereof.

Cephems of formula (I) defined under the present  
5 invention are known compounds or can be prepared from  
known compounds by known methodologies.

For example, suitable methods for the preparation of  
the claimed compounds can be found in the following  
bibliographic references, listed according to the site  
10 of functionalization of the cephem nucleus:

2-substituted cephems: Noveau Journal de Chimie 1, 85  
(1977); Synthetic Communications 15, 681 (1985); Chem.  
Pharm. Bull. 31, 1482 (1983); Bull. Chem. Soc. Jpn. 56,  
2185 (1983); Tetrahedron Letters 21, 1293, (1980); J.  
15 Org. Chem. 44, 811 (1979); Tetrahedron Letters 4751  
(1978); J. Am. Chem. Soc. 100, 1886 (1978); J. Chem.  
Soc. Perkin I 2298 (1977); Tetrahedron Letters 3611  
(1977); J. Chem. Soc. Chem. Comm. 671 (1973);  
Tetrahedron Letters 3717 (1972); US 3.660.395; Eur. J.  
20 Med. Chem. 24, 599 (1989); J. Med. Chem. 14, 420  
(1971); J. Med. Chem. 14, 426 (1971); Heterocycles 29,  
1107 (1989); J. Med. Chem. 27, 1225 (1984).

3-substituted cephems: Heterocycles 24, 1653 (1986); J.  
Chem. Soc. Perkin I 1361 (1991); SynLett 389 (1990);  
25 SynLett 391 (1990); J. Org. Chem. 55, 5833 (1990);  
Tetrahedron Letters 31, 3389 (1983); Tetrahedron 41,  
2025 (1985); Chem. Pharm. Bull. 33, 5534 (1985); J.

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Chem. Soc. Perkin I 2281 (1983); J. Org. Chem. 53, 983 (1988); Gazz. Chim. II. 115, 169 (1985); Tetrahedron 39, 461 (1983); J: Antibiotics 39, 380 (1986); J. Am. Chem. Soc. 108, 1685 (1986); J. Chem. Soc. Chem. Comm. 5 1012 (1974); Chem. Pharm. Bull. 28, 2116 (1980); Gazz. Chim. IC 110, 519 (1980); Phil. Trans. R. Soc. Lond. B 289, 173 (1980); Chem. Pharm. Bull. 28, 62 (1980); J. Antibiotics 37, 1441 (1984); Tetrahedron Letters 29, 6043 (1988); Tetrahedron Letters 29, 5739 (1988);  
10 Heterocycles 1799 (1986); J. Org. Chem. 54, 5828 (1989); J. Antibiotics 42, 159 (1989); Heterocycles 28, 657 (1989); SynLett 888 (1991); J. Antibiotics 43, 533 (1990), Eur. J. Med. Chem. 27, 875 (1992).  
4-substituted cephems: Tetrahedron Letters 52, 5219  
15 (1978); Tetrahedron Letters 33, 2915 (1977); J. Org. Chem. 51, 4723 (1986); Synthesis 52 (1986); J. Org. Chem. 35, 2429 (1970); J. Org. Chem. 35, 2430 (1970); US 4992-541-A; EP 0124001-A2; EP 0267723-A2; US 20 4.547.371; J. Med. Chem. 33, 2522 (1990); Tetrahedron Letters 32, 6207 (1991); Eur. J. Med. Chem. 27, 875 (1992), J. Med. Chem. 20, 173 (1977); J. Med. Chem. 15, 1172 (1972); US 5.077.286; PCT WO 89/10926.  
7-substituted cephem: J. Org. Chem. 43, 3788 (1978); J. Org. Chem. 42, 2960 (1977); J. Org. Chem. 42, 3972  
25 (1977); Tetrahedron Letters 1303 (1976); J. Med. Chem. 25, 457 (1982); Tetrahedron Letters 16, 1441 (1979); J. Chem. Soc. Chem. C mm. 276 (1988); J. Chem. Soc. Perkin

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I 635 (1987); J. Org. Chem. 54, 3907 (1989); J. Antibiotics 52, 159 (1989); Tetrahedron Letters 30, 2375 (1989); Tetrahedron Letters 30, 2379 (1989) Thetrahedron Letters 375 (1972); Tetrahedron Letters 19, 1637 (1979).

As stated above, the compounds of the invention have been found to be active as anti-metastatic agents. Accordingly, they can be used in mammals, including humans, for preventing and/or treating the metastatic spread of tumors.

The antimetastatic activity of the compounds was proved experimentally in vivo against the highly metastatic B16F10 murine melanoma. B16F10 tumor cells were maintained in vitro by serial soil. For experimental purpose, tumor cells were pretreated in vitro with 1000 $\gamma$  for 6 hrs, whereas control were incubated with medium. Cells were then harvested and injected intravenously into C57/B16 mice at the concentration of 10<sup>5</sup> cells/mouse. Animals were treated intraperitoneally with the compound for 6 days at the dose of 200 mg/kg. After 22 days mice were sacrificed and the number of lung metastatic foci were counted.

Data reported in table 1 show that a representative compound of the invention, namely (6R,7S)-2-(2,2-dimethyl-propionyl)-4-(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-[1,2,4]triazin-3-ylsulfanyl)-7-methoxy-3-methyl-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-

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one (internal code FCE26238) is clearly active as antimetastatic agent. An evident reduction of the metastasis number was observed after in vitro pretreatment and after in vivo treatment. No evidence  
5 of toxicity was observed.

Table 1

Group	Treatment with FCE26238		median number of metastasis (range)
	in vitro	in vivo	
Control	-	-	20 (7-72)
	-	200 mg/kg x6	4 (2-24)
	1000γ x 6 hrs	-	0 (0-0)
	1000γ x 6 hrs	200 mg/kg x6	0 (0-0)

The compounds of the invention can be administered by  
10 the usual routes, for example, parenterally, e.g. by intravenous injection or infusion, intramuscularly, subcutaneously, topically or orally, intravenous injection or infusion being the preferred. The dosage depends on the age, weight and condition of the patient  
15 and on the administration route.

A suitable dosage for the compounds of the invention, e.g. FCE26238 for administration to adult humans may

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range from about 0.5 to about 300 mg per dose 1-4 times a day.

The pharmaceutical compositions of the invention may contain a compound of formula (I) or a pharmaceutically acceptable salt thereof, as the active substance, in association with one or more pharmaceutically acceptable excipients and/or carriers.

5 The pharmaceutical compositions of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form. For instance, solutions for intravenous injection or infusion may contain as carrier, for example, sterile water or, preferably, they may be in the form of sterile aqueous isotonic saline solutions.

10 15 Suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride.

20 In the form for topical application, e.g. creams, lotions or pastes for use in dermatological treatment, the active ingredient may be mixed with conventional oleoginous or emulsifying excipients.

25 The solid oral forms, e.g. tablets and capsules, may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn

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starch and potato starch; lubricants, e.g. silica,  
talc, stearic acid, magnesium or calcium stearate,  
and/or polyethylene glycols; binding agents, e.g.  
starches, arabic gums, gelatin, methylcellulose,  
5 carboxymethyl cellulose, polyvinylpyrrolidone;  
disaggregating agents, e.g. a starch, alginic acid,  
alginates, sodium starch glycolate; effervesing  
mixtures; dyestuffs; sweeteners; wetting agents, for  
instance, lecithin, polysorbates, laurylsulphates; and,  
10 in general, non-toxic and pharmacologically inactive  
substances used in pharmaceutical formulations. Said  
pharmaceutical preparations may be manufactured in a  
known manner, for example by means of mixing,  
granulating, tabletting, sugar-coating, or film-coating  
15 processes.

An object of the invention is also to provide a method  
of treatment of the above mentioned pathological  
conditions comprising both separate and substantially  
contemporaneous administration of a composition  
20 containing a compound of formula (I), or a  
pharmaceutically acceptable salt thereof, and a  
pharmaceutical composition containing a different  
pharmaceutically active agent, typically an antitumor  
agent.

25 Antitumor agents that can be formulated with a compound  
of the invention or, alternatively, can be administered  
in a combined method of treatment are e.g. doxorubicin,

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daunomycin, epirubicin, idarubicin, etoposide, fluorouracil, paclitaxel, melphalan, cyclophosphamide, bleomycin, vinblastin and mitomycin or a mixture of two or more thereof.

5 The compounds of the invention can therefore be used in a treatment to ameliorate a cancer.

EXAMPLE A

Tablets:

			Per 10,000
	<u>Ingredients</u>	<u>Per Tablet</u>	<u>Tablets</u>
10	1. Active ingredient Cpd of Form I	40.0 mg	400 g
	2. Corn Starch	20.0 mg	200 g
	3. Alginic acid	20.0 mg	200 g
	4. Sodium alginate	20.0 mg	200 g
15	5. Magnesium Stearate	<u>1.3 mg</u>	<u>13 g</u>
		101.3 mg	1013 g

Procedure for tablets:

Step 1. Blend ingredients No. 1, No. 2, No. 3 and No. 20 4 in a suitable mixer/blender .

Step 2. Add sufficient water portionwise to the blend from Step 1 with careful mixing after each

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addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

Step 3. The wet mass is converted to granules by  
5 passing it through an oscillating granulator using a number 8 mesh (2.38) screen.

Step 4. The wet granules are dried in an oven at 60°C until dried.

Step 5. The dried granules are lubricated with  
10 ingredient no. 5.

Step 6. The lubricated granules are compressed on a suitable tablet press.

Example B

Intramuscular injection:

15	<u>Ingredients</u>	<u>Per ml</u>	<u>Per liter</u>
	1. Active ingredient	10.0 mg	10 g
	Cpd of Form I		
	2. Isotonic buffer	q.s.	q.s.
	solution pH 4.0.		

20

Procedure:

Step 1. Dissolve the active ingredient in the buffer solution.

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Step 2. Aseptically filter the solution from step 1.

Step 3. The sterile solution is aseptically filled  
into sterile ampoules

Step 4. The ampoules are sealed under aseptic  
conditions

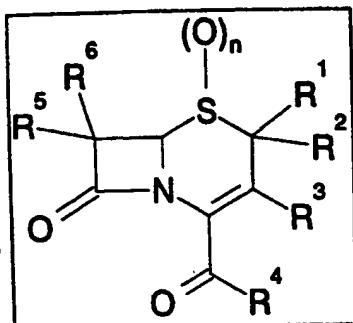
5

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CLAIMS

1. The use of a compound of formula (I)

(I)



5       wherein n is zero, one or two;

R<sup>1</sup> is hydrogen or an optionally substituted C<sub>1</sub>-C<sub>12</sub> alkyl, C<sub>2</sub>-C<sub>12</sub> alkenyl, C<sub>2</sub>-C<sub>12</sub> alkynyl, C<sub>6</sub>-C<sub>10</sub> aryl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>5</sub>-C<sub>8</sub> cycloalkenyl, or C<sub>7</sub>-C<sub>14</sub> aralkyl,  
10       C<sub>8</sub>-C<sub>14</sub> aralkenyl,      C<sub>8</sub>-C<sub>14</sub> aralkynyl,  
          (cycloalkyl)alkyl,    (cycloalkyl)alkenyl,  
          heterocyclyl,          (heterocyclyl)alkyl,  
          (heterocyclyl)alkenyl;

R<sup>2</sup> represents an atom or group selected from the following:

15       (1) halogen  
          (2) R<sup>1</sup> as defined above  
          (3) an ether OR<sup>1</sup> wherein R<sup>1</sup> is as defined above  
          (4) a thioether, sulphoxide or sulphone -S(O)<sub>n</sub>R<sup>1</sup>  
           wherein n and R<sup>1</sup> are as defined above  
          (5) acyloxy -OC(O)R<sup>1</sup> wherein R<sup>1</sup> is as defined above;  
          (6) sulphonyloxy -OS(O)<sub>2</sub>R<sup>1</sup> wherein R<sup>1</sup> is as defined

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above;

or R<sup>1</sup> and R<sup>2</sup> taken together form a methylene group of formula =CHR<sup>1</sup> or =CH-CO<sub>2</sub>R<sup>1</sup> or =CH-COR<sup>1</sup> wherein R<sup>1</sup> is as defined above; or R<sup>1</sup> and R<sup>2</sup> taken together with the C-2 carbon atom of the cephem nucleus constitute a carbocyclic or heterocyclic group; R<sup>3</sup> represents one of the following:

- (1) R<sup>2</sup> as defined above
- (2) an acyl group -C(O)R<sup>1</sup>, -C(O)OR<sup>1</sup> or -CO<sub>2</sub>H  
wherein R<sup>1</sup> as defined above
- (3) an oxymethyl group -CH<sub>2</sub>-OR<sup>1</sup> wherein R<sup>1</sup> is as defined above
- (4) a thiomethyl group or a derivative thereof of formula -CH<sub>2</sub>S(O)<sub>n</sub>R<sup>1</sup> wherein n and R<sup>1</sup> are as defined above
- (5) an acyloxymethyl group -CH<sub>2</sub>OC(O)R<sup>1</sup> wherein R<sup>1</sup> is as defined above or a -CH<sub>2</sub>O-R<sup>7</sup> wherein R<sup>7</sup> is a mono, di- or tripeptide composed of D or L  $\alpha$ -aminoacids chosen from Ala, Gly, Val, Leu, Ile, Phe and with the terminal amino group either free or protected as an amide -NHCOR<sup>1</sup> or sulfonamide -NHSO<sub>2</sub>R<sup>1</sup> wherein R<sup>1</sup> is as defined above
- (6) an acylthiomethyl group -CH<sub>2</sub>SC(O)R<sup>1</sup> wherein R<sup>1</sup> is as defined above
- (7) a sulphonyloxymethyl group -CH<sub>2</sub>-OSO<sub>2</sub>R<sup>1</sup> wherein R<sup>1</sup> is as defined above

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(8) a group of formula  $-\text{CH}_2-\text{Z}-\text{NR}^1\text{R}^8$  wherein Z is  
a bond,  $-\text{O C(O)}-$  or  $-\text{OS(O)}_2-$ ,  $\text{R}^1$  is as defined  
above and  $\text{R}^8$ , being the same or different, is  
as defined above for  $\text{R}^1$ ; or  $\text{R}^1$  and  $\text{R}^8$  taken  
5 together with the nitrogen atom to which they  
are attached represent a heterocyclic ring;

(9) ammoniomethyl  $-\text{CH}_2\text{N}^+\text{R}^1\text{R}^8\text{R}^9$  wherein  $\text{R}^1$  and  $\text{R}^8$  are  
as defined above and  $\text{R}^9$ , being the same or  
different, is as defined for  $\text{R}^1$ ; or  $\text{R}^1$  is  
10 alkyl and  $\text{R}^8$  and  $\text{R}^9$  together with the nitrogen  
atom to which they are attached represent a  
heterocyclic ring;

$\text{R}^4$  is either:

(1) a group  $\text{R}^1$  wherein  $\text{R}^1$  is as defined above  
15 (2) a group  $\text{OR}^1$  wherein  $\text{R}^1$  is as defined above  
(3) a group  $\text{SR}^1$  wherein  $\text{R}^1$  is as defined above  
(4) a group  $\text{NR}^1\text{R}^5$  wherein  $\text{R}^1$  and  $\text{R}^8$  are as defined  
above;

$\text{R}^5$  is either  $\text{R}^1$  as defined above or halogen or  $\text{C}_1\text{-C}_6$   
20 alkoxy,  $\text{C}_1\text{-C}_6$  alkylthio or  $\text{C}_1\text{-C}_6$  acylamino;

$\text{R}^6$  is a group selected from the following:

(1)  $\text{R}^2$  as defined above  
(2) a group of formula  $-\text{Z-N}(\text{R}^1)\text{R}^8$  wherein Z,  $\text{R}^1$  and  
 $\text{R}^8$  are as defined above  
25 (3) a group of formula  $-\text{NR}^8\text{C(O)R}^1$  wherein  $\text{R}^1$  and  $\text{R}^8$   
are as defined above, or  $\text{R}^1$  and  $\text{R}^8$  taken  
together with the aminocarbonyl group to

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which they are attached constitute a heterocyclic ring

(4) an acylamino group  $-NHR^7$  wherein  $R^7$  is as defined above

5 (5) an ammonio group  $-N^+R^1R^8R^9$  wherein  $R^1$ ,  $R^8$  and  $R^9$  are as defined above;

or  $R^5$  and  $R^6$  taken together with the C-7 carbon atom of the cephem nucleus constitute a carbocyclic or heterocyclic ring;

10 or  $R^5$  and  $R^6$  taken together constitute a methylene group of formula  $=CHR^1$ ,  $=CH-CO-R^1$  or  $=CH-SO_2R^1$ , wherein  $R^1$  is as defined above, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in preventing and/or treating the metastatic spread of tumors.

15 2. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 1 in preventing and/or treating the metastatic spread of tumors.

20 3. The use of a compound of formula (I), according to claim 1 or 2 , wherein the compound is selected from

(6R,7S)-2-(2,2-dimethyl-propionyl)-4-(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-[1,2,4]triazin-3-ylsulfanyl)-7-methoxy-3-methyl-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]ct-2-en-8-one,

25 2-benzoyl-7-methoxy-4-(5-methyl-[1,3,4]thiadiazol-

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2-ylsulfanyl)-3-(5-methyl-[1,3,4]thiadiazol-2-  
ylsulfanymethyl)-5,5-dioxo-5-thia-1-aza-  
bicyclo[4.2.0]oct-2-en-8-one,  
2-(2,2-dimethyl-propionyl)-7-methoxy-4-(1-methyl-  
5  
1H-tetrazol-5-ylsulfanyl)-3-(1-methyl-1H-tetrazol-  
5-ylsulfanymethyl)-5,5-dioxo-5-thia-1-aza-  
bicyclo[4.2.0]oct-2-en-8-one,  
2-benzoyl-4-(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-  
[1,2,4]triazin-3-ylsulfanyl)-7-methoxy-3-methyl-  
10  
5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-  
one,  
2-benzoyl-7-methoxy-3-methyl-4-(1-methyl-1H-  
tetrazol-5-ylsulfanyl)-5,5-dioxo-5-thia-1-aza-  
bicyclo[4.2.0]oct-2-en-8-one,  
2-(2,2-dimethyl-propionyl)-7-methoxy-3-methyl-4-  
15  
(5-methyl-[1,3,4]thiadiazol-2-ylsulfanyl)-5,5-  
dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one,  
2-(2,2-dimethyl-propionyl)-7-methoxy-4-(5-methyl-  
[1,3,4]thiadiazol-2-ylsulfanyl-3-(5-methyl-  
20  
[1,3,4]thiadiazol-2-ylsulfanymethyl)-5,5-dioxo-5-  
thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one,  
2-benzoyl-7-methoxy-4-(1-methyl-1H-tetrazol-5-  
ylsulfanyl)-3-(1-methyl-1H-tetrazol-5-  
ylsulfanymethyl)-5,5-dioxo-5-thia-1-aza-  
25  
bicyclo[4.2.0]oct-2-en-8-one,  
7-allyl-2-benzoyl-4-(5-methyl-[1,3,4]thiadiazol-1-  
2-ylsulfanyl)-3-(5-methyl-[1,3,4]thiadiazol-2-

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ylsulfanyl methyl)-5,5-dioxo-5-thia-1-aza-  
bicyclo[4.2.0]oct-2-en-8-one,  
7-allyl-2-(2,2-dimethyl-propionyl)-4-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanyl)-3-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanyl methyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one,  
5 3-(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-[1,2,4]triazin-3-ylsulfanyl methyl)-7-methoxy-5,5-dioxo-2-(pyrrolidine-1-carbonyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one,  
10 1-(3-acetoxymethyl-7-methoxy-5,5,8-trioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-enane-2-carbonyl)pyrrolidine-2-carboxilic acid,  
15 1-[3-acetoxymethyl-5,5,8-trioxo-7-(2,2,2-trifluoro-ace tylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-enane-2-carbonyl]-pyrrolidine-2-carboxilic acid,  
20 1-(7-benzoylamino-3-methyl-5,5,8-trioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-enane-2-carbonyl)-pyrrolidine-2-carboxylic acid,  
25 3-methyl-5,5,8-trioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 4-carboxy-benzyl ester,  
2-benzoyl-7-ethylsulfanyl-4-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanyl)-3-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanyl methyl)-5,5-dioxo-5-thia-1-aza-bicycl [4.2.0]oct-2-en-8-one,

- 32 -

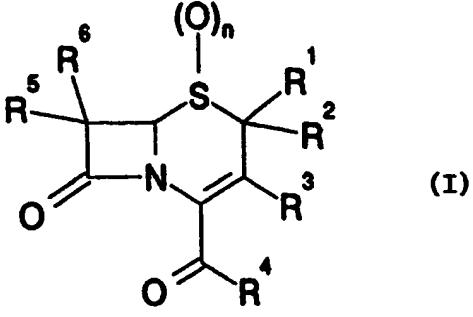
2-benzoyl-7-ethylsulfanyl-3-methyl-4-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one,  
3-(1-methyl-1H-tetrazol-5-ylsulfanylmethyl)-5,5,8-trioxo-7-(2,2,2-trifluoro-acetylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 4-carboxy-benzyl ester,  
2-acetylamino-3-[7-methoxy-3-(1-methyl-1H-tetrazol-5-ylsulfanylmethyl)-5,5,8-trioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-enane-2-carbonylsulfanyl]-propionic acid,  
2-acetylamino-3-[7-allyl-3-(1-methyl-1H-tetrazol-5-ylsulfanylmethyl)-5,5,8-trioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-enane-2-carbonylsulfanyl]-propionic acid or a pharmaceutically acceptable salt thereof.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: <b>PCT/EP94/02059</b> (22) International Filing Date: <b>24 June 1994 (24.06.94)</b>  (30) Priority Data: <b>9314562.1 14 July 1993 (14.07.93) GB</b>		(81) Designated States: AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(71) Applicant (for all designated States except US): <b>PHARMACIA S.P.A. [IT/IT]; Via Robert Koch, 1.2., I-20152 Milan (IT).</b>  (72) Inventors; and (75) Inventors/Applicants (for US only): <b>ALPEGIANI, Marco [IT/IT]; Via Tolmezzo, 12/5, I-20132 Milan (IT). BIS-SOLINO, Pierluigi [IT/IT]; Via Roma, 36/2, I-27020 San Giorgio di Lomellina (IT). PERRONE, Ezio [IT/IT]; Via Aldo Moro, 44, I-20010 Boffalora Ticino (IT). PESENTI, Enrico [IT/IT]; Viale Visconti, 9, I-20093 Cologno Monzese (IT).</b>		Published <i>With international search report.</i> (88) Date of receipt of the international search report: <b>9 March 1995 (09.03.95)</b>	
(54) Title: <b>USE OF CEPHEM DERIVATIVES AS ANTI-METASTATIC AGENTS</b>			
(57) Abstract			
<p>The present invention relates to the use of known cephem derivatives of formula (I), wherein n is zero, one or two; R<sup>1</sup> is hydrogen or an organic radical, R<sup>2</sup> represents halo or an organic radical or R<sup>1</sup> and R<sup>2</sup> taken together with the C-2 carbon atom of the cephem nucleus constitute a carbocyclic or heterocyclic group; R<sup>3</sup> represents R<sup>2</sup> as defined above or an organic radical, R<sup>4</sup> is either R<sup>1</sup> or an organic group, R<sup>5</sup> is either R<sup>1</sup> as defined above or halo or C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylthio or C<sub>1</sub>-C<sub>6</sub> acylamino; R<sup>6</sup> is R<sup>2</sup> as defined above or an organic group, or pharmaceutically acceptable salt thereof.</p>			
 <p style="text-align: right;">(I)</p>			

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**INTERNATIONAL SEARCH REPORT**

International application No <b>PCT/EP 94/02059</b>
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<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 6 C07D501/00 A61K31/545
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According to International Patent Classification (IPC) or to both national classification and IPC
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<b>B. FIELDS SEARCHED</b>
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Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D A61K
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
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<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>
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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	GB,A,2 266 525 (MERCK & CO., INC.) 3 November 1993 see page 1, line 17 - page 1, line 28; claims 1-10 ---	1-3
Y	PATENT ABSTRACTS OF JAPAN vol. 15, no. 256 (C-0845) 28 June 1991 & JP,A,03 083 987 (FUJISAWA PHARMACEUT. CO. LTD.) 9 April 1991 see abstract ---	1-3
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Herz, C
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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No  
**PCT/EP 94/02059**

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